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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MAHATAN, CHANNING	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 12/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/729,838	LEWIS, HAL A.	
	Examiner	Art Unit	
	Channing S Mahatan	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *43-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2 Sheets* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

APPLICANTS ELECTION

Applicants' election, with traverse, of Group I (claims 1-42; drawn to a crystal, a method of making the crystal and a machine-readable medium embedded with the information that corresponds to a three-dimensional representation of the crystal) and SEQ ID NO: 1 is acknowledged. Applicants traverse the PTO's further sequence election requirement applicable to Groups I-III. Upon further consideration the Examiner is withdrawing the sequence election requirement and SEQ ID NOs: 1, 2, and 3 will be examined in the context of Group I.

CLAIMS UNDER EXAMINATION

Claims herein under examination are claims 1-42. Claims 43-53 are withdrawn from prosecution as directed to a non-elected invention.

Claims Rejected Under 35 U.S.C. § 112 1st

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

SCOPE OF ENABLEMENT

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 U.S.P.Q. 546 (B.P.A.I. 1986) and reiterated by the Court of Appeals in In re Wands, 8 U.S.P.Q. 2d 1400 at 1404 (C.A.F.C. 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the

prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claims 1-31 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the *H. pylori* LuxS (SEQ ID NO: 1) crystal with tetragonal unit cell and space group symmetry $P4_32_12$ and unit cell dimensions of a=71.04 +/-0.7 Å, b=71.04 +/-0.7 Å, c=130.14 +/-1.3 Å., *H. influenzae* LuxS (SEQ ID NO: 2) crystal with tetragonal unit cell and space group symmetry $P4_22_12$ and unit cell dimensions of a=129.59 +/-1.3 Å, b=129.59 +/-1.3 Å, c=53.74 +/-0.5 Å, and *D. radiodurans* LuxS (SEQ ID NO: 3) crystal monoclinic unit cell and space group symmetry $P2_1$ with unit cell dimensions of a=43.71 +/-0.4 Å, b=82.18 +/-0.8 Å, c=49.48 +/-0.5 Å and beta=102.78 +/-1.0 degrees or C2 monoclinic unit cell is observed with dimensions of a=51.19+/-0.5 Å, b=70.14 +/-0.7 Å, c=49.73 +/-0.5 Å and beta=112.03 +/-1.1 degree and methods of making these specific crystals (indicated below), however, does not reasonably provide enablement for <u>any</u> crystal of LuxS in crystalline form and the method of making <u>any</u> LuxS crystal thereof.

The specification indicates Applicants are in possession of the following specific crystals of LuxS:

> "The *H. pylori* LuxS crystals of the present invention are generally characterized by a diffraction pattern, as shown in FIG. 2. The crystals are further characterized by unit cell dimensions and space group symmetry information obtained from the diffraction patterns, as described above. The crystals, which may be native crystals, heavy-atom derivative crystals or co-crystals, have a

tetragonal unit cell and space group symmetry $P4_32_12$. In one form of crystalline *H. pylori* LuxS, the unit cell has dimensions of a=71.04 +/-0.7 Å, b=71.04 +/-0.7 Å, c=130.14 +/-1.3 Å." (page 18, lines 6-12; Figure 2; Table 7)

"The *H. influenzae* LuxS crystals, which may be native crystals, heavy-atom derivative crystals or co-crystals, have a tetragonal unit cell and space group symmetry $P4_22_12$. In one form of crystalline *H. influenzaei* LuxS, the unit cell has dimensions of a=129.59 +/-1.3 Å, b=129.59 +/-1.3 Å, c=53.74 +/-0.5 Å." (page 36, lines 15-19; Figure 3; Table 8)

"In one form, the *D. radiodurans* LuxS crystals, which may be native crystals, heavy-atom derivative crystals or co-crystals, have a monoclinic unit cell and space group symmetry $P2_1$. The unit cell has dimensions of a=43.71 +/-0.4 Å, b=82.18 +/-0.8 Å, c=49.48 +/-0.5 Å and beta=102.78 +/-1.0 degrees...In another form of *D. radiodurans* LuxS crystals, a C2 monoclinic unit cell is observed with dimensions of a=51.19 +/-0.5 Å, b=70.14 +/-0.7 Å, c=49.73 +/-0.5 Å and beta=112.03 +/-1.1 degree." (pages 36-37, lines 22-28 and 1-2, respectively; Figures 4 and 5; Table 9)

The specification further indicates specific conditions (method of making) particular for each of the said above particular crystals of LuxS:

"sitting drops comprising about 1 µL of *H. pylori* LuxS polypeptide (5 mg/mL in 10 mM HEPES, pH 7.5, 150 mM sodium chloride, 10 mM methionine, 1 mM beta-mercaptoethanol) with 1 µL reservoir solution (32% w/v PEG 1000, 200 mM ammonium sulfate, and 100 mM MES, pH 5.75) suspended over 0.5 mL reservoir solution for about one week at 20°C. provide diffraction quality crystals." (pages 32-33, lines 26-29 and 1, respectively)

"sitting drops prepared by mixing about 1 µL of *D. radiodurans* LuxS polypeptide (19 mg/mL in 10 mM HEPES, pH 7.5, 150 mM sodium chloride, 10 mM methionine, 1 mM beta-mercaptoethanol) and 1 µL reservoir solution (26% w/v PEG monomethyl ether ("PEG MME") 5000, and 100 mM MES, pH 6.5) suspended over 0.5 µL reservoir solution for about one week at 4°C provide diffraction quality crystals." (page 33, lines 2-6)

> "Sitting drops prepared by mixing about 1 μL of *H. influenzae* LuxS polypeptide (10 mg/mL in 10 mM HEPES, pH 7.5, 150 mM sodium chloride, 10 mM methionine, 1 mM beta-mercaptoethanol) and 1 μL reservoir solution (21% w/v PEG MME 5000, and 100 mM Bis-Tris, pH 6.25) suspended over 0.5 mL reservoir solution for about one week at 12°C. provide diffraction quality crystals." (page 33, lines 6-10)

However, the specification fails to disclose other LuxS crystals and suitable conditions for the crystallization of "LuxS". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In the field of protein crystallography, it is well established that the utilization of a variety of crystallization methods, for the protein in question, greatly improves the chances of identifying suitable conditions for crystallization. However, obtaining suitable single crystal(s) is the least understood step in the X-ray structural analysis of a protein(s). Therefore, since the science of protein crystallization is underdeveloped, the crystallization of a protein is mainly a trial-and-error procedure. Further, it is well known that the homologous proteins from different sources cannot be easily crystallized using the same techniques and/or conditions and may result in different crystal forms. See, for example, Jan Drenth ("Principles of Protein X-ray Crystallography", pages 1-9). Additionally, Lewis et al. (A Structural Genomics Approach to the Study of Quorum Sensing: Crystal Structures of Three LuxS Orthologs. Structure. June 2001, Volume 9, pages 527-537) indicate the difficulty within the current state of the art to obtain any crystal structures of LuxS (page 528, right column, lines 19-24) and state "We are unable to obtain crystals from the *C. jejuni* LuxS protein, perhaps in part because of its very high solubility (160 mg/ml)" (page 536, left column, lines 18-20).

While working examples are not, per se, required, the specification must provide an enabling disclosure for the invention as it is claimed such that one of skill in the art could practice the invention without undue experimentation. Proper disclosure for the specific conditions for crystallization (i.e. pH, concentration of protein, reagents, etc) is required for enablement of any crystal of LuxS. For example, Applicants have disclosed specific structural characteristics (i.e. unit cell dimension, space group, etc) pertaining to a crystal and specific conditions for the method of making a crystal of *H. pylori* LuxS when comparing to *H. influenzae* LuxS and/or *D. radiodurans* LuxS (refer to above citation within the original disclosure). The specification establishes that specific conditions for the method of making any LuxS crystal are not universal. Additionally, claims 11-14 recite specific unit cell dimensions for the "crystal comprising LuxS in crystalline form". These unit cell dimensions are disclosed in the specification as corresponding specifically to the unit cell dimensions of *H. pylori* LuxS (SEQ ID NO: 1) (claim 11), *H. influenzae* LuxS (SEQ ID NO: 2) (claim 12) or *D. radiodurans* LuxS (SEQ ID NO: 3) (claims 13 and 14) as indicated above. Instant claims 11-14, as currently presented, are directed any "crystal comprising LuxS in crystalline form" with these specific unit cell dimensions and not to the specific SEQ ID NOs that are indicated in the specification. The specification establishes that unit cell dimensions are not the same for any crystal comprising LuxS in crystalline form (i.e. *H. pylori*, *H. influenzae*, *D. radiodurans*). Therefore, one of skill in the art could not make and/or use the invention without further undue experimentation to obtain any crystal of LuxS. Thus, the above level of disclosure is not present here, nor supplied by the art or knowledge of one skilled in the art, therefore, the breadth of the claims is not enabled.

Claims Rejected Under 35 U.S.C. § 112 2nd

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 6, 8, 10, 34, 37, and 39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

VAGUE AND INDEFINITE

Claims 3 (line 1), and 34 (lines 1-2) recite the phrase limitation "diffraction quality" which is vague and indefinite. It is acknowledged the specification defines diffraction quality crystal as:

> "a crystal that is well-ordered and of a sufficient size, i.e., at least 10 μm, preferably at least 50 μm, and most preferably at least 100 μm in its smallest dimension such that it produces measurable diffraction to at least 3 Å resolution, preferably to at least 2.4 or 1.8 Å resolution, and most preferably to at least 1.5 Å resolution or greater resolution. Diffraction quality crystals include native crystals, heavy-atom derivative crystals, and co-crystals."

However, the specification provides only that a crystal be "well-ordered and of sufficient size" and thus the definition provided for in the specification is so broadly encompass that its' definition is unclear. It should be noted while the example exemplify particular range of sizes and resolutions such values are absent from the instant claim. Clarification of the metes and bounds, via clearer claim language, is requested.

Claims 6 (line 1), and 37 (lines 1-2) recite the phrase limitation "LuxS is a mutant" which is vague and indefinite. While it is acknowledged the specification defines LuxS mutant as:

> "a polypeptide characterized by an amino acid sequence that differs from the wild-type sequence by the substitution of at least one amino acid residue of the wild-type sequence with a different amino acid residue and/or by the addition and/or deletion of one or more amino acid residues to or from the wild-type sequence. The additions and/or deletions can be from an internal region of the wild-type sequence and/or at either or both of the N- or C-termini. A mutant may have, but need not have, LuxS activity. Preferably, a mutant displays biological activity that is substantially similar to that of the wild-type LuxS."

It is unclear the limitation Applicants regard mutant LuxS to be, wherein it is absent the criteria/parameters by which a polypeptide is considered mutant LuxS. For example, amino acid substitutions/additions/deletions have no limitations (i.e. can be alter to any polypeptide) nor is it required that the mutant LuxS have LuxS activity. Clarification of the metes and bounds, via clearer claim language, is requested.

Claims 8 (line 1) and 39 (lines 1-2) recite the phrase limitation "conservative mutant" which is vague and indefinite. While it is acknowledged the specification defines conservative mutant as:

> "a mutant in which at least one amino acid residue from the wild-type sequence is substituted with a different amino acid residue that has similar physical and chemical properties, i.e., an amino acid residue that is a member of the same class or category, as defined above. For example, a conservative mutant may be a polypeptide that differs in amino acid sequence from the wild-type sequence by the substitution of a specific aromatic Phe (F) residue with an aromatic Tyr (Y) or Trp (W) residue."

It is unclear the limitation Applicants regard as a "conservative mutant", wherein it is absent the criteria/parameters by which a polypeptide is considered a "conservative mutant" of LuxS. For example, the definition provided for fails to limit the degree of amino acid substitution and

therefore every amino acid may be substituted, thus altered to be another polypeptide not limited to LuxS polypeptides. Clarification of the metes and bounds, via clearer claim language, is requested.

Claim 10 (line 2) recites the phrase "substantially similar" which is vague and indefinite. The phrase "substantially similar" implies a criteria/range of values/degree considered similar which is unclear. Applicants can resolve this issue by particularly pointing out the criteria/range of values/degree by which the diffraction pattern is considered "substantially similar". Clarification of the metes and bounds, via clearer claim language, is requested.

Claims Rejected Under 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following excerpt is from M.P.E.P. § 2106 Section VI "DETERMINE WHETHER THE CLAIMED INVENTION COMPLIES WITH 35 U.S.C. § 102 AND 103" (particular emphasis on bolded areas) and is applied to the below 35 U.S.C. § 102 rejection, wherein the "information that corresponds to a three-dimensional structural representation of a crystal comprising LuxS in crystalline form or a fragment or a portion thereof" (claim 32, lines 2-3) is considered "non-functional descriptive" material (i.e. mere arrangement of data; failing to satisfy the practical application requirement). Further, examples are provided for in the M.P.E.P. regarding situations of nonfunctional descriptive material.

> As is the case for inventions in any field of technology, assessment of a claimed computer-related invention for compliance with 35 U.S.C. 102 and 103 begins with a comparison of the claimed subject matter to what is known in the prior art. **If no differences are found between the claimed invention and the prior art, the claimed invention lacks novelty and is to be rejected by Office personnel under 35 U.S.C. 102.** Once distinctions are identified between the claimed invention and the prior art, those distinctions must be assessed and resolved in light of the knowledge possessed by a person of ordinary skill in the art. Against this backdrop, one must determine whether the invention would have been obvious at the time the invention was made. If not, the claimed invention satisfies 35 U.S.C. 103. Factors and considerations dictated by law governing 35 U.S.C. 103 apply without modification to computer-related inventions. Moreover, merely using a computer to automate a known process does not by itself impart nonobviousness to the invention. See Dann v. Johnston, 425 U.S. 219, 227-30, 189 USPQ 257, 261 (1976); In re Venner, 262 F.2d 91, 95, 120 USPQ 193, 194 (CCPA 1958).
>
> If the difference between the prior art and the claimed invention is limited to descriptive material stored on or employed by a machine, Office personnel must determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material, as described supra in paragraphs IV.B.1(a) and IV. B.1(b). Functional descriptive material is a limitation in the claim and must be considered and addressed in assessing patentability under 35 U.S.C. 103. Thus, a rejection of the claim as a whole under 35 U.S.C. 103 is inappropriate unless the functional descriptive material would have been suggested by the prior art. In re Dembiczak, 175 F.3d 994, 1000, 50 USPQ2d 1614, 1618 (Fed. Cir. 1999). **Nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious. Cf. In re Gulack, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983) (when descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in terms of patentability).** Common situations involving nonfunctional descriptive material are:
>
> - a computer-readable storage medium that differs from the prior art solely with respect to nonfunctional descriptive material, such as music or a literary work, encoded on the medium,
>
> - a computer that differs from the prior art solely with respect to nonfunctional descriptive material that cannot alter how the machine functions (i.e., the descriptive material does not reconfigure the computer), or
>
> - a process that differs from the prior art only with respect to nonfunctional descriptive material that cannot alter how the process steps are to be performed to achieve the utility of the invention.
>
> Thus, if the prior art suggests storing a song on a disk, merely choosing a particular song to store on the disk would be presumed to be well within the level of ordinary skill in the art at the time the invention was made. The difference between the prior art and the claimed invention is simply a rearrangement of nonfunctional descriptive material.

Claims 32-42 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Gronbech-Jensen et al.

Gronbech-Jensen et al. describes a machine (i.e. computer) having memory capable of storing/containing data (Column 5, lines 26-27; Columns 10-11, lines 55-67 and 1-23,

respectively; and Figure 2). The authors further provide for a computer readable medium as in instant claims 32-42 (Column 30-32, lines 34-67, 1-42, and 1-40, respectively; Claims 29-44). All limitations concerning the type of data are given no patentable weight as they are considered to be non-functional descriptive material. Thus, Gronbech-Jensen et al. clearly anticipates the claimed invention.

Claims Rejected Under 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

It should be noted that Hampton Research (Tel. No. 949-425-1321), contacted on 30 September 2002, indicated Crystal Screen™ was available for sale beginning 1991. Thus, the date of sale justifies the applicability of the above reference for the below 35 U.S.C. § 103 Rejections.

Claims 1, 3, 4, 6, 8, 15-23, and 25-31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bassler et al. (U.S. Patent Number 6,559,176) taken in view of Crystal Screen™ (Hampton Research).

Bassler et al. discloses various LuxS polypeptides (i.e. *H. pylori*, *H. influenzae*, etc) (Columns 18-22). The inventors state several uses for the LuxS proteins, particularly

overproduction of LuxS proteins would allow one to make a quantity sufficient for crystallization (Column 21, lines 55-56). Obtaining a crystal structure of the LuxS proteins would enable determination of the LuxS active site that produces the naturally-occurring autoinducer-2, and could therefore be used for computer-aided design of autoinducer-2 analogs, LuxS inhibitors, and rational drug design (Column 21, lines 56-61). However, Bassler et al. fails to disclose crystallization methods and the crystal of LuxS polypeptides.

Crystal Screen™ is a complete reagent kit designed to provide rapid a screening method for the crystallization of biological molecules (i.e. proteins, etc) and allows for the determination of crystallization conditions (page 1, Column 1, lines 1-4). Procedures for performing the screen and obtaining crystals is set forth, wherein crystals are incubated between 4°C and room temperature (pages 1-2, beginning on Column 1, line 11; claims 22 and 31). The attached Crystal Screen™ Scoring Sheet lists numerous solutions/conditions for obtaining a crystal comprising a solution/conditions. Applicants are directed to Crystal Screen 2 Reagent Formulation listing various salt reagents/conditions (i.e. ammonium sulfate; claims 20 and 29), buffer reagents/conditions (i.e. HEPES at various pH levels; claims 18, 19, 21, 27, 28, and 30), and precipitant reagents/conditions (i.e. polyethylene glycol; claims 16, 17, 25, and 26).

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the invention to practice Bassler et al. (U.S. Patent Number 6,559,176), LuxS polypeptides (i.e. *H. pylori*, *H. influenzae*, etc) with Crystal Screen™, determination of crystallization conditions for a biological molecule (i.e. protein) and obtaining a crystal of a biological molecule. Bassler et al. (U.S. Patent Number 6,559,176) again states obtaining a crystal structure of the LuxS proteins would enable determination of the LuxS active site that produces the naturally-occurring

autoinducer-2, and could therefore be used for computer-aided design of autoinducer-2 analogs, LuxS inhibitors, and rational drug design (Column 21, lines 56-61). Crystal Screen™ is also effective in determining the solubility of a molecule in a wide rage of precipitants and pH (page 1, Column 1, lines 4-5).

Claims 1, 3-8, 15-23, and 25-31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bassler et al. (U.S. Patent Number 6,559,176) taken in view of Crystal Screen™ (Hampton Research) further in view of Leonard et al. (U.S. Patent Number 5,700,660).

Bassler et al. (U.S. Patent Number 6,559,176) and Crystal Screen™ (Hampton Research) are applied as stated above. However, Bassler et al. and Crystal Screen™ fail to teach LuxS mutant is a seleomethionine or selenocysteine mutant (i.e. heavy-atom derivative).

Leonard et al. (U.S. Patent Number 5,700,660) describes the method of substituting methionine residue or cysteine residue with a selenomethionine or selenocysteine. Leonard et al. state: "X-ray crystallography is used to determine the three-dimensional structure of polypeptides, but is often hampered by the inability of the investigator to unambiguously identify specific regions of the polypeptide without iterative, computer intensive calculations of repetitive X-ray diffraction patterns. Heavy atoms, having an atomic mass of greater than 20, are often added to the polypeptide during crystallization in an attempt to provide a point of reference, since these atoms provide unique signature(s) in multi-wavelength anomalous diffraction (MAD) and multiple isomorphous replacement (MIR) analysis." (Columns 1-2, lines 56-68 and 1-13). Further, such substitutions with these heavy atoms are added to the crystal randomly, or at most or all locations of a certain amino acid throughout the polypeptide, e.g., a replacement of all

methionines in a protein with a selenomethionine or a replacement of all cysteines in a protein with a selenocysteine (Column 2, lines 34-40 and 51-67).

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the invention to practice Bassler et al. (U.S. Patent Number 6,559,176), LuxS polypeptides (i.e. *H. pylori*, *H. influenzae*, etc) with Crystal Screen™, determination of crystallization conditions for a biological molecule (i.e. protein) and Leonard et al. (U.S. Patent Number 5,700,660) substitution of methionine residue or cysteine residue with selenomethionine or selenocytsteine thereby obtaining a mutant useful that provides one of ordinary skill in the art to identify specific regions of the polypeptide without iterative, computer intensive calculations of repetitive X-ray diffraction patterns.

INFORMATION DISCLOSURE STATEMENT

The "Information Disclosure Statement(s)" contains several cited references that have been line through because copies of said references were absent and thus could not be considered. Should Applicants desire consideration of the said lined through references a new 'Information Disclosure Statement' and a copy of said references is requested. It should be noted the International Search Report corresponding to PCT/US/30684 was lined through because such information is not publicly available.

OBJECTION TO DISCLOSURE

The disclosure is objected to because of the following informalities:

The disclosure is objected to because of embedded hyperlinks and/or other form of browser-executable code within the specification (page 44, lines 14, 16, and 21). Such hyperlinks and/or browser-executable code are impermissible in the text of the application as

they represent an improper incorporation by reference. See M.P.E.P. §608.01 and 608.01(p). A suggested format is:

"World Wide Web address:rcsb.org/pdb/docs/format/pdbguide2.2/guide2.2_frame.html"

The disclosure is objected because of a misspelling on page 36, line 15, wherein "*H. influenzaei*" should be replaced with "*H. influenzae*".

Appropriate Correction Is Requested.

No Claims Are Allowed.

EXAMINER INFORMATION

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 C.F.R. § 1.6(d)). The CM1 Fax Center number is either (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Channing S. Mahatan whose telephone number is (703) 308-2380 (until 12 January 2004) and (571) 272-0717 (after 12 January 2004). The Examiner can normally be reached on M-F (8:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina M. Plunkett, whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

Date: November 30, 2003

Examiner Initials: CSM

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